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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,484	02/05/2001	John H. Griffin	SCRIP1200-1	8867

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	15

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/777,484	GRIFFIN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *17-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 09 April 2003 (Paper No. 12) has been entered in full.

This application contains claims 16-17 drawn to a species nonelected with traverse in Paper No. 8 (01 July 2002). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-16 and 19-21 are under consideration in the instant application, as they read upon the elected species of "stroke", "NMDA receptor antagonist", and "anticoagulant".

Withdrawn Objections and/or Rejections

1. The objection to the specification at pg 3 of the previous Office Action (Paper No. 9, 07 October 2002) is *withdrawn* in view of the amended Brief Description of Drawings (Paper No. 12, 09 April 2003).

2. The rejection of claims 1-2, 9-10, and 15 under 35 U.S.C. § 102(b) as set forth at pg 7-8 of the previous Office Action (Paper No. 9, 07 October 2002) is *withdrawn* in view of Applicant's persuasive arguments (Paper No. 12, 09 April 2003).

3. The supplemental information disclosure statement filed on 21 April 2003 (Paper No. 14) has been considered.

Claim Rejections - 35 USC § 112

4. Claims 1-16 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing brain infarction volume and edema volume in a subject suffering from a stroke comprising administering to the subject an

effective amount of activated protein C (APC) to thereby decrease brain infarction volume and edema volume in the subject, does not reasonably provide enablement for a method of protecting neuronal cells from cell death in a subject having or at risk of having a neuropathological disorder comprising administering to the subject, a neuroprotective amount of activated protein C (APC). The specification is not enabling for a method of reducing inflammation in a subject having or at risk of having a neuropathological disorder by administering APC. The specification is also not enabling for a method of reducing inflammation in a subject having or at risk of having inflammatory vascular disease comprising administering APC. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Furthermore, the dependent claims recite that APC is administered intravenously during the stroke or up to 6 hours before or after the stroke. The claims recite that the method further comprises administering one or more anti-thrombotic factors, APC-cofactors, one or more additional neuroprotective agents (such as a N-methyl-D-aspartate receptor (NMDA) antagonist), one or more anti-coagulants, and one or more anti-inflammatory agents. The claims also recite that the APC cofactor is Protein S. The basis for this rejection is set forth at pg 3-6 of the previous Office Action (Paper No. 9, 07 October 2002).

Applicant's arguments (Paper No. 12, 09 April 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that working examples are provided as the data set forth in the Examples explicitly illustrate that administration of activated protein C (APC) protects neuronal cells from cell death. Applicant argues that the data in Examples 1 and 2 demonstrate that

treatment with APC either before or after induction of stroke protected mice from accelerated stroke-related death and restored cerebral blood flow during middle cerebral artery occlusion (pg 30-31). Applicant concludes that administration of APC results in significant reduction in brain injury with a concomitant improvement in neurological performance. Applicant states that therefore, those skilled in the art would readily acknowledge that the specification enables methods for protecting neuronal cells from cell death.

Applicant's arguments have been fully considered but are not found to be persuasive. As mentioned in the previous Office Action, the Examiner has interpreted the term "protecting" in claim 1 to mean that an activity will not occur, i.e. neuronal cell death will not occur. Although Example 1 of the specification teaches that mice with induced stroke who are treated with APC have increased cerebral blood flow during pre-occlusion, occlusion, and reperfusion and have increased survival time and motor neurologic scores at 24 reperfusion compared to stroke, untreated control mice, these results do not necessarily indicate that neuronal cells are being protected from cell death by APC. The specification does not teach any methods or working examples that indicate the survival differences between *neurons* in control and APC-treated mice. For example, there are no experiments in which neurons are examined histologically or immunologically to determine whether the APC-treated mice had statistically the same number of neurons as normal (non-stroke) control mice and statistically increased numbers of neurons as compared to stroke, untreated mice.

Furthermore, there is little or no guidance in the specification to indicate that administration of APC would be able to "protect" neuronal cells from cell death in subjects having or at risk of having all possible neuropathological disorders. Examples 1-3 in the

specification teach that mice are subjected to a modified middle cerebral artery occlusion technique to induce acute focal ischemic stroke with cerebrovascular thrombosis (pg 25, lines 16-21). Thus, Examples 1-3 of the specification utilize a mouse model for stroke. However, stroke has a different pathophysiology from other neuropathological disorders, such as Alzheimer's disease, Huntington's disease, epilepsy, multiple sclerosis, etc. (pg14, lines 31-32; pg 15, lines 1-2), which are all neuropathological diseases encompassed by the claims. Many neuropathological diseases such as Alzheimer's disease and Huntington's disease, among others, have also proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000; Steece-Collier et al., Proc Natl Acad Sci USA 99(22): 13972-13974, 2002; Feigin et al. Curr Opin Neurol 15: 483-489, 2002). Therefore, undue experimentation would be required of the skilled artisan to administer APC to subjects with all possible neuropathological disorders and protect neuronal cells from cell death. A large quantity of experimentation would also be required be one skilled in the art to identify a subject population at risk of having all possible neuropathological disorders that required the administration of APC.

The specification of the instant application also does not teach any methods or working examples that administer any additional factors or agents in conjunction with APC, other than Protein S. Undue experimentation would be required of the skilled artisan to determine the optimal quantity of all possible neuroprotective agents, anti-thrombotic factors, anti-coagulant agents, and anti-inflammatory agents to be administered to a subject with APC. The skilled artisan would also not be able to predict the effect these various agents would have upon the subject when combined with APC.

(ii) Applicant asserts that the specification includes working examples to indicate that administration of APC to a subject reduces inflammation. Applicant contends that the specification provides data which demonstrates that administration of APC reduces volumes of brain infarction and edema by 59% and 50%, respectively (pg 10, lines 3-4, 18-24; pg 33, lines 22-26).

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the Examiner acknowledges that administration of APC decreases brain infarction volume and edema volume in a subject suffering from a stroke. However, according to the state of the art, brain infarction and edema are not measurements of inflammation. For example, a brain infarction is the formation of infarct in the brain, an area of tissue death due to local lack of oxygen (see Appendix A; MedicineNet.com, http://www.medterms.com/script/main/art.asp?ArticleKey=3970). Edema is the swelling of tissue as a result of excess water accumulation (see Appendix B; MedicineNet.com; http://www.medterms.com/script/main/art.asp?ArticleKey=3192).

Additionally, the specification does not teach any methods or working examples that indicate the administration of APC reduces inflammation in a subject having or at risk of having all possible neuropathological disorders. The specification of the instant application does not teach any methods or working examples to indicate that the administration of APC reduces inflammation in a subject having or at risk of having all possible inflammatory vascular diseases. A large quantity of experimentation would also be required be one skilled in the art to identify a subject population at risk of having all possible inflammatory vascular diseases that required the administration of APC.

(iii) Applicant asserts that undue experimentation would not be required to determine the optimal quantity of APC administration, the best administration route, the duration of treatment, and possible side effects produced by administration of APC. Applicant submits that those skilled in the art would readily acknowledge that these factors are all simply administration protocols which vary depending on the disease being treated and the size and general health of the subject undergoing treatment. Applicant argues that any alleged "experimentation" required to optimize these factors would only be routine experimentation, and therefore would not rise to the level of undue experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". The specification outlines large dosage ranges of APC, several different methods of administration, and various lengths of treatment (pg 20-22). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily protect neuronal cells from cell death or reduce

inflammation in a subject by administration of APC with all possible dosages, administration routes, and durations of treatment.

(iv) The declaration under 37 CFR 1.132 filed 09 April 2003 (Paper No. 10) has been considered the Examiner.

Declarants and co-inventors, John Griffin and Berislav Zlokovic, indicate that the specification discloses APC treatment either before or after induction of stroke protected mice from accelerated stroke-related death and restored cerebral blood flow during middle artery occlusion. Declarants also indicate that administration of APC reduced volumes of brain infarction and edema by 59% and 50%, respectively. Declarants state that in Exhibit A, they demonstrate that APC directly activates anti-apoptotic pathway in ischemic brain endothelial cell through protease activated receptor-1 (PAR-1) and endothelial protein C receptor. Declarants mention that in Exhibit B, they demonstrate that APC reduces NMDA-induced apoptosis in mouse cortical neurons by blocking tumor suppressor protein p53, normalization of the proapoptotic *Bax/Bcl-2* ratio and reduction in caspase-3 signaling. Declarants indicate that they demonstrate APC's neuroprotective effects on cortical neurons and prevention of NMDA excitotoxicity in mice *in vivo* require PAR-1 and PAR-3 on neurons.

However, the declaration under 37 CFR 1.132 filed 09 April 2003 (Paper No. 10) is insufficient to overcome the rejection of claims 1-16 and 19-21 based upon lack of enablement under 35 U.S.C. § 112, first paragraph, as set forth in the previous Office Action. Specifically, Exhibit A (Cheng et al., Nature 9(3): 338-342, 2003) indicates that APC inhibits apoptosis in hypoxic human brain endothelium *in vitro*, by inhibition of p53, normalization of the

proapoptotic *Bax/Bcl-2* ratio and reduction in caspase-3 signaling. The experiments in Exhibit A are performed *in vitro*, rather than *in vivo,* as required by the claims. The experiments in Exhibit A also utilize brain endothelial cells rather than neurons, as required by the claims. Although the reference in Exhibit A further elucidates the mechanism of APC in brain endothelial cells, one skilled in the art would not be able to predict that the experiments performed in Exhibit A would protect neurons from cell death in a subject or reduce inflammation in a subject. This Exhibit does not indicate that neurons are "protected" from cell death by administration of APC to a subject, as recited by the claims. This Exhibit also does not teach a method of reducing inflammation in a subject, as recited by the claims.

Additionally, the manuscript of Exhibit B indicates that APC reduces NMDA-induced apoptosis in mouse cortical neurons and induces the expression of anti-apoptotic genes. However, this Exhibit, like Exhibit A, only further elucidates the mechanism of action of APC. This Exhibit does not indicate that neurons are "protected" from cell death *in vivo* by administration of APC to a subject, as recited by the claims. This Exhibit also does not teach a method of reducing inflammation in a subject, as recited by the claims.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to "protect" neuronal cells from cell death and to reduce inflammation in a subject having or at risk of having a neuropathological disease or inflammatory vascular disease, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of administering all possible neuroprotective agents, anti-thrombotic factors, anti-coagulant agents, or anti-inflammatory agents, undue experimentation

would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

5. Claims 1-16 and 19-21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The term "neuroprotective amount" in claims 1-8, 16, and 19-21 is a relative term which renders the claim indefinite. The term "neuroprotective amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The appropriate dosage range of APC that is required to "protect" neuronal cells from cell death in a subject cannot be determined.

7. The term "anti-inflammatory effective amount" in claims 9-16 and 19-21 is a relative term which renders the claim indefinite. The term "anti-inflammatory effective amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The appropriate dosage range of APC that is required to reduce inflammation in a subject cannot be determined.

Applicant's arguments (Paper No. 12, 09 April 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that when these phrases are construed in light of the specification, it is clear that "neuroprotective amount" and anti-inflammatory effective amount" refer to dosages

which vary depending on the disease being treated and on the size and general health of the subject undergoing treatment. Applicant argues that those skilled in the art are able to determine appropriate dosage ranges by routine manipulation of standard administration protocols, which are set forth in detail in the specification.

Applicant's arguments have been fully considered but are not found to be persuasive because it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Therefore, the claims are still rejected as being indefinite because the claims do not clearly define "neuroprotective amount" and anti-inflammatory effective amount". (Please note this issue could be overcome by removing the term "neuroprotective" and "anti-inflammatory effective" from the claims.)

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
June 26, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER